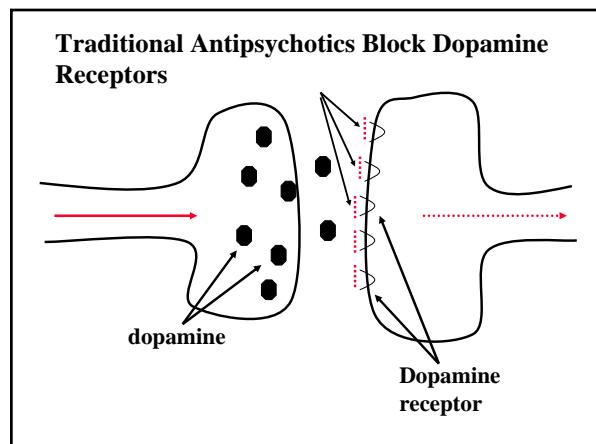
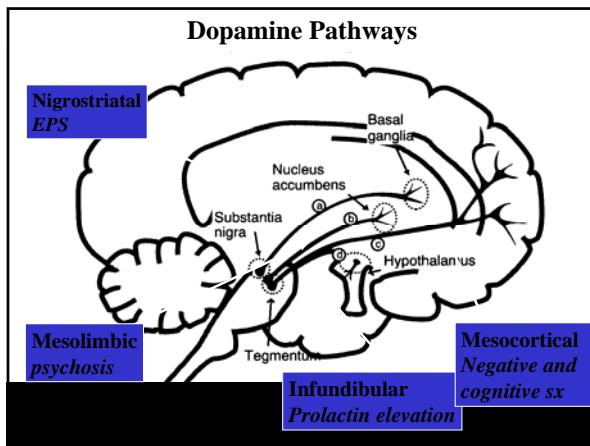


- There Are Many Different Neurotransmitters**
- Dopamine
 - Acetylcholine (cholinergic)
 - Noradrenalin (adrenergic)
 - Serotonin (5-HT or 5-hydroxy-tryptamine)
 - GABA (gamma-aminobutyric acid)
 - Glutamate

Dopamine Receptors
 D_1, D_2, D_3, D_4, D_5

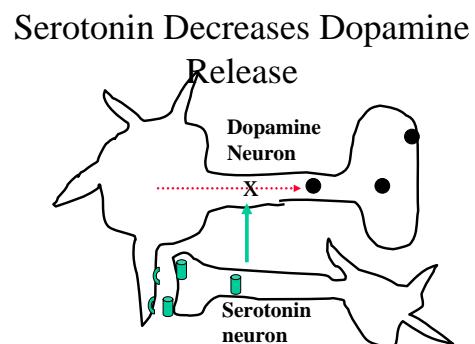
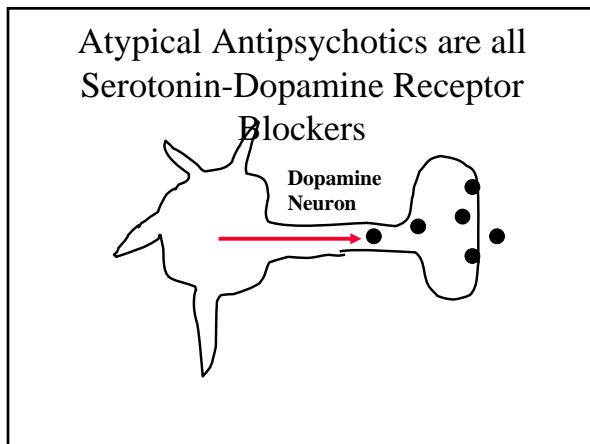
Serotonin Receptors
 $5HT_{1A}, 5HT_{2A}, 5HT_{2C}$,
 $5HT_3, 5HT_4, 5HT_{XXXX}$



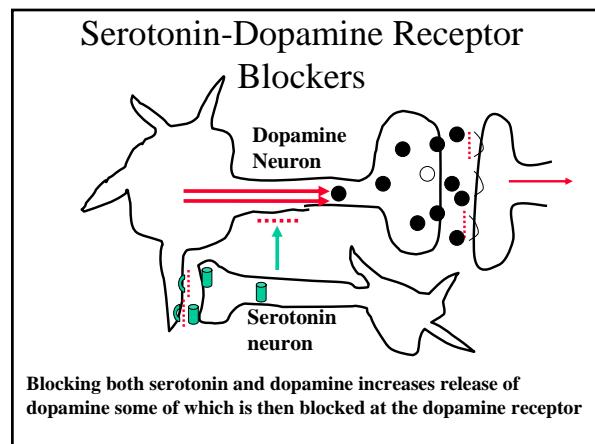
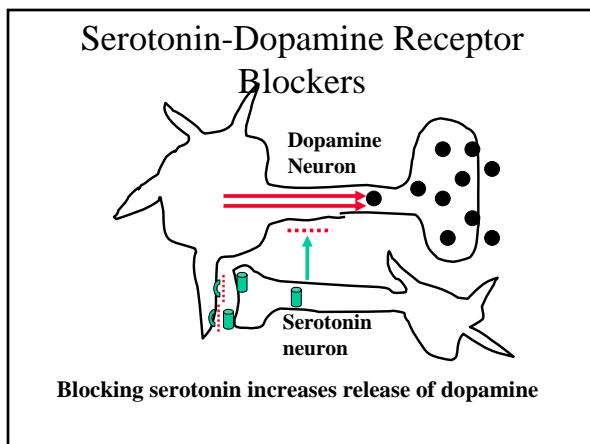


Antipsychotic Medications

- Traditional antipsychotic medications--block dopamine receptors
- Atypical antipschotic medications--block both dopamine and serotonin receptors
- Atypical antipsychotic medications are less “sticky” at the receptor--come and go rather than get glued on



Serotonin blocks transport and release of dopamine



Clozapine

Very complicated pharmacology

- Many side effects
 - Weight Gain
 - Anticholinergic
 - Sedation
 - Seizures
 - Agranulocytosis
 - Heat Related Deaths
- Very effective
 - positive and negative
 - good mood stabilizer
 - very low EPS
 - very low TD

Clozapine

M1--anticholinergic

- dry mouth
- constipation
- blurred vision
- drowsiness
- memory impairment

Alpha adrenergic
Low BP, dizziness

H1 Antihistamine

- Drowsiness
- Weight gain

5HT_{2C} Blockers

- Weight Gain

Adapted from Stahl
Essential Psychopharmacology

Risperidone (Risperdal)

- Dose related EPS
 - Less is better
 - Prolactin Elevation
 - Weight Gain
- Positive and negative efficacy
- Mood stabilizer
- Decreased TD

Adapted from Stahl
Essential Psychopharmacology

Olanzapine (Zyprexa)

- Some dose related EPS
- Slight prolactin Elevation
- Big Weight Gain
- Diabetes (?)
- Somewhat sedating
- Positive and negative efficacy
- Mood stabilizer
- Decreased TD

Adapted from Stahl
Essential Psychopharmacology

Quetiapine (Seroquel)

- More is Better
 - 400 mg up to 1200 mg
 - Very low EPS
 - Very low TD risk
 - Some weight gain
 - Sedating
 - Needs dose titration to decrease dizziness
- Low dose may be useful in people with borderline disorder

Adapted from Stahl
Essential Psychopharmacology

Ziprasidone (Geodon)

Newest antipsychotic
NO WEIGHT GAIN
Very low diabetes risk
Higher dose often better than low

QTc prolongation
Activating/agitating
Antidepressant activity

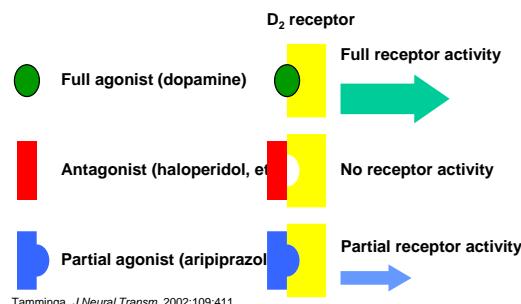
Nausea, sleep disturbance
EPS dose related

Adapted from Stahl
Essential Psychopharmacology

Aripiprazole (Abilify)

- Dopamine agonist/antagonist
- Appears to cause little or no weight gain, little EPS, little sedation and little effect on heart function

Intrinsic Activity: Ability to Stimulate Receptors



Antipsychotic Side Effects

Weight gain and diabetes

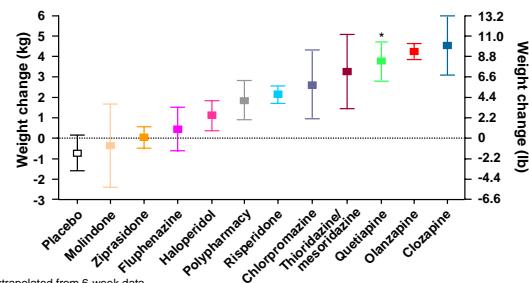
Major health risk!

- Related to serious mental illness
- Life style
- Obesity
- Medications

Weight gain and diabetes are the "TD" of the atypical antipsychotic medications

Mean Change in Weight With Antipsychotics

Estimated Weight Change at 10 Weeks on "Standard" Dose



BMI: Body Mass Index

$$\text{BMI} = \frac{\text{kg}}{\text{m}^2} = (703) \frac{\text{lbs}}{\text{inches}^2}$$

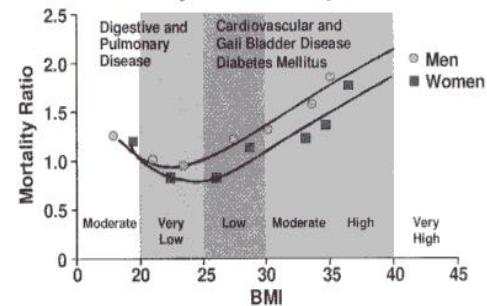
Ex: 5'8", 160 lbs = BMI of 24.3

5'8", 195 lbs = BMI of 29.6

5'8", 220 lbs = BMI of 33.4

Antipsychotics

Obesity and Mortality Risk



Relative Risk of Weight Gain and Diabetes

Medication	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine (Clozaril)	+++	+	+
Olanzapine (Zyprexa)	+++	+	+
Risperidone (Risperdal)	++	??	??
Quetiapine (Seroquel)	++	??	??
Aripiprazole (Abilify)	+/-	-	-
Ziprasidone	+/-	-	-

Diabetes Care 27(2) Feb 2004 596-601

Consensus Recommendations on Diabetes Monitoring

	Baseline	4 wks	8 wks	12 wks	3 mos	12 mos	5 yrs
Personal/Family Hx	X					X	
Weight (Body Mass Index)	X	X	X	X	X	X	X
Waist Circumference	X					X	
BP	X			X		X	
Fasting Glucose	X			X		X	
Fasting lipid profile	X						X

Diabetic Care Feb 2004

Metabolic Syndrome: 3 or more following factors:

Abdominal obesity

Waist circumference of > 40 inches in men
 Waste circumference of > 35 inches in women

HDL cholesterol (measured after 12 hours fast)

[LDL = bad cholesterol : low HDL = good cholesterol]
 HDL cholesterol < 40 mg/dl in men
 HDL cholesterol < 50 mg/dl in women

Elevated triglycerides > 150 mg/dl

Elevated blood pressure >130/85 mm Hg

Fasting blood glucose >110 mg/dl

NCEP III Circulation 2002 106: 3143-3421

Traditional Antipsychotic Medications

Examples

- fluphenazine (Prolixin)
- haloperidol (Haldol)

Both available as long acting injection

Traditional D₂ blocker may (??) work better in some patients

Much less expensive

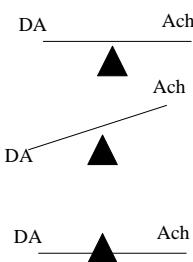
Differences between newer and older medications recently called into question by new data (CATIE)

Antipsychotic Side Effects

EPS (Extrapyramidal [muscle] side effects)

- Dystonias (muscle cramps)
- Tremor--coarse Parkinsonian type tremor
- Akinisia--decreased movement/spontaneity
- Akathisia--motor restlessness
- Tardive Dyskinesia: MAY BE PERMANENT

Extrapyramidal Side Effects and Anticholinergic Medications



Dopamine and Acetylcholine Are normally in balance

When dopamine is blocked,
 This system goes out of balance

Blocking acetylcholine with
 an anticholinergic medication
 puts system back in balance

Antipsychotic Side Effects common--not life threatening

- Psychotoxic side effects
 - Depression, sedation, confusion, dysphoria
- Anticholinergic
 - Dry mouth, constipation, blurred vision, memory impairment, confusion
- Alpha-adrenergic
 - dizziness
- Increase Prolactin
 - Breast engorgement, sexual side effects

NMS: Neuroleptic Malignant Syndrome

Usually within 30 days of new medication or ↑ dose

- Hyperthermia (fever)
- Muscle rigidity
- Tremor, myoclonus (muscle jerks)
- Confusion, stupor
- Increased heart rate, labile blood pressure
- Rapid breathing, shortness of breath
- Sweating, sialorrhea, incontinence
- Elevated CPK, leukocytosis, metabolic acidosis

Antipsychotic Medications

Traditional Indications

- Schizophrenia
- Mania/ mood stabilization
- Agitated or psychotic depression
- Psychosis associated with dementia
- Drug induced psychosis

Other possible indications

- Agitation
- Severe OCD
- Anxiety with cognitive disorganization

Sales of Antipsychotic Meds [2005]

	FDA approval	Patent Expires	2005 sales
Risperdal	1993	2007	2.31 billion
Olanzapine	1996	2011	2.54 billion
Quetiapine	1997	2011	2.6 billion
Ziprasidone	2001	2012	685 million
Aripiprazole	2002	2014	1.54 billion

Psychiatric News May 19, 2006

New Antipsychotic Medications

Paliperidone	metabolite of risperidone	janssen	2006
Bifeprunox	partial dopamine agonist	wyeth	2007
Asenapine	adrenergic partial agonist	prizer	2007
Iloperidone	dopamine/serotonin antagonist	titan	2008
Sertindole	dopamine/serotonin antagonist	lundbeck	2008
Olanzapine	depot	Lilly	2008
Zotepine	dopamine/serotonin/ adrenergic antagonist	Orion	2008